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Effect of Intraperitoneal Chemotherapy and Fibrinolytic Therapy on Tumor Implantation in Wound Sites

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Failure of surgical treatment for gastrointestinal cancers is often caused by recurrence of the tumor in traumatized peritoneal surfaces. This study examined the effect of intraperitoneal administration of doxorubicin and recombinant tissue plasminogen activator (rt-PA), a fibrinolytic agent, on incidence and volume of postoperative tumor implants in peritoneal wounds. Prior to randomization, a surgical wound was created on the right parietal peritoneum of 110 BDIX rats and 6×10^5 DHD/K12 colon cancer cells were inoculated intraperitoneally (ip). The control group was given an intraperitoneal injection of saline. Five groups received 1 mg/kg of ip doxorubicin at different times postoperatively: at the end of surgery (D0), 3 hr after surgery (D+3), postoperative day 1 (D1), postoperative day 3 (D3), and postoperative day 7 (D7). In a second set of experiments, five groups of rats received, in addition to postoperative doxorubicin, 5 mg/kg of intraoperative ip rt-PA. Incidence and volume of tumor implants in peritoneal wounds were assessed for each group 20 days after the tumor inoculation. All rats of the control group (incidence = 100%) developed tumor implants in peritoneal wounds. Mean (SD) volume was 16.2 (4.7) mm^3. When administered at D0, D+3, and D1 intraperitoneal doxorubicin reduced significantly the incidence and volume of tumor implants in wounds. Postoperative administration of doxorubicin at D3 and D7 did not affect significantly the incidence and the volume of tumor implants in peritoneal wounds. When rt-PA was administered intraoperatively, ip injection of doxorubicin at any postoperative timing decreased significantly the incidence and volume of tumor implants. In conclusion, ip doxorubicin administered before postoperative D3 may act on tumor cell implanted in peritoneal wounds. Delayed (D3, D7) ip administration of doxorubicin does not prevent the development of tumor implants in peritoneal wounds. Intraoperative administration of rt-PA may significantly increase the efficacy of delayed ip chemotherapy.

KEY WORDS: **wound, tumor implantation, intraperitoneal chemotherapy, fibrinolytic therapy, doxorubicin**

INTRODUCTION

The failure of primary surgical treatment of abdominal or pelvic malignancies is often marked by cancer recurrence in areas of surgical dissection and trauma [1–3]. The mechanism whereby a large proportion of patients have recurrent disease confined to the resection sites may be related to the implantation of tumor cells disseminated within the peritoneal cavity prior to or during surgical resection. Experimental studies have suggested that surgical trauma promotes tumor implantation [4–6]. For abdominal and pelvic malignancies, the peritoneum which

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covers both parietal and visceral structures represents the most common site for surgical trauma and treatment failure.

Various adjuvant and neoadjuvant chemotherapy protocols have been used in an effort to improve local-regional control of abdominal and pelvic tumors. When treating these tumors with systemic chemotherapy, both the magnitude of drug exposure to the tumor cells and the duration of this drug exposure are limited by systemic toxicity. Local–regional administration of cytostatic drugs has been considered as a logical step in order to obtain a higher drug concentration in the target tissues with lower systemic toxicity. For intra-abdominal malignancies, intraperitoneal chemotherapy is the logical route for regional administration [7,8]. The pharmacological rationale of intraperitoneal chemotherapy has been demonstrated. Because of their limited transperitoneal absorption, the intraperitoneal concentration of selected drugs may be 18–620 times higher than the systemic drug levels as a result of intraperitoneal instillation [9].

However, the effectiveness of intraperitoneal chemotherapy appears to be dependent on the timing of drug administration in relation to the surgical event. In clinical trials, intraperitoneal chemotherapy administered soon after the cancer resection or in the early postoperative period altered significantly the natural history of patients with gastric cancer [10]. When administered few weeks after the surgery, regional chemotherapy resulted in no impact [11]. This time-dependent effectiveness of therapy may be explained, in part, by the "tumor cell entrapment" hypothesis [12]. This hypothesis states that during the early stages of wound healing, plasma proteins extravasate and form a deposit in which tumor cells may be entrapped. The retention of tumor cells in the wound matrix depends on their binding to the cell-adhesive proteins. Once tumor cells have adhered to the wound matrix, they are embedded by connective tissue. The resulting scar may act as a protective coat shielding the tumor cells from direct contact with intraperitoneally administered drugs [13]. Considering that fibrin represents the most important component of this matrix, it follows that fibrinolytic agents may decrease tumor cell entrapment [14]. Different fibrinolytic agents have previously been tested for the prevention of tumor implantation in liver wounds [15]. Recombinant tissue-plasminogen activator (rt-PA) emerged as one of the most effective fibrinolytic agent.

The present study was designed to evaluate the effect of intraperitoneal doxorubicin and rt-PA on tumor implantation and tumor growth in peritoneal wounds in a rat model. First, the influence of time between tumor inoculation in surgical wound and the administration of intraperitoneal doxorubicin was determined by the assessment of incidence and volume of tumor implants in the peritoneal wound. The second part of the study investigated the possible role of fibrinolytic therapy (rt-PA) in increasing the effectiveness of intraperitoneal doxorubicin to prevent tumor implantation in wounds.

MATERIALS AND METHODS

Animals

BDIX male rats weighing 180–220 g were obtained from a single breeding colony (Charles River Laboratories, Wilmington, MA). Animals were individually housed and were allowed free access to food and water.

Cell Lines

The cloned tumor cell line used in the present experiments, DHD/K12/Prob, originated from a colon carcinoma induced by 1,2-dimethylhydrazine in a BDIX strain rat [16]. Cancer cells were cultivated in Ham-F10 medium (Microbiological Associates, Walkersville, MA) supplemented by 10% fetal calf serum (FCS) (Gibco Laboratories, Grand Island, NY) and 40 μg/ml of Penicillin/Streptomycin/Gentamycin (Gibco Laboratories, Grand Island, NY), which will be called complete medium. The cells were counted using trypan blue exclusion as a test of viability.

Procedures

Rats were anesthetized with an intramuscular injection of sodium phenobarbital (50 mg/kg). A midline laparotomy was performed and a wound (1-cm^2 surface) was created on the peritoneum of the right abdominal wall using an electrocoagulator (Harvard Apparatus, South Natick, MA). Each corner of the wound square was tattooed with trypan blue in order to easily identify the wounded peritoneal area at the time of tumor assessment. Before closure of the abdomen, the animals received an intraperitoneal injection of 6×10^5 viable tumor cells in 3 ml of complete medium.

Experimental Design

Experiment 1. This experiment was designed to evaluate the effect of intraperitoneal doxorubicin and its timing of administration on tumor implantation in peritoneal wounds. A control group of rats (n = 10) received intraperitoneal injection of saline solution (5 ml) at the end of surgery. Five groups of 10 rats were then randomly assigned to receive an intraperitoneal injection of doxorubicin (doxorubicin hypochloride, BenVenue Laboratories, Bedford, OH) at different postoperative time: at the end of surgery (D0), 3 hr after surgery (D+3), postoperative day 1 (D1), postoperative day 3 (D3), and postoperative day 7 (D7). Doxorubicin was administered at a dose of 1 mg/kg diluted in 5 ml of saline solution.

Experiment 2. This experiment was designed to evaluate the effect of rt-PA on tumor implantation in peritoneal wounds. Ten rats which received an intraperitoneal injection of rt-PA (Activase, Genentech, San Francisco, CA) at the end of the surgery were compared to the control group. rt-PA was administered at a dose of 5

mg/kg. Such intraperitoneal dose of rt-PA has been shown to increase the level of intraabdominal plasminogen and decrease the level of systemic fibrinogen in rats [17,18].

Experiment 3. This experiment was designed to evaluate the effect of rt-PA plus intraperitoneal doxorubicin on tumor implantation in peritoneal wounds. Five groups of 10 rats were randomly assigned to receive an intraperitoneal injection of doxorubicin (1 mg/kg) at different postoperative time: at the end of surgery (D0), 3 hours after surgery (D+3), postoperative day 1 (D1), postoperative day 3 (D3), and postoperative day 7 (D7). All rats received, in addition to doxorubicin, an intraperitoneal injection of rt-PA (5 mg/kg) at the end of surgery.

Data Analysis

All animals were sacrificed 20 days after the surgical procedure. A midline laparotomy was performed. The number of rats with tumor implants in peritoneal wound was recorded. Tumor burden was assessed by counting and measuring with calipers the width (W) and length (L) of each tumor implant present in the wounded area. Tumor volumes were calculated using the formula $L \times W^2$. For all experiments, incidences of tumor implantation were compared between control group and treated groups using the Fisher's test. Tumor volumes in peritoneal wounds were compared between control group and treated groups with the Wilcoxon Rank Test. All statistical analysis were conducted using SAS for Windows, version 6.8 (SAS Institute, Cary, NY). For all statistical analysis, values for $P < 0.05$ were taken as significant.

RESULTS

Experiment 1: Effect of the Timing of Intraperitoneal Doxorubicin Administration on Tumor Implantation (Fig. 1)

Incidence of implantation. All rats (100%) in control group exhibited tumor in peritoneal wound. Five rats (50%) of group D0, 4 rats (40%) of group D+3, 5 rats (50%) of group D1, 8 rats (80%) of group D3, and 8 rats (80%) of group D7 demonstrated tumor deposit in the peritoneal wound. Rats treated with doxorubicin before postoperative day 3 had a significantly lower incidence of tumor implantation compared to the control group. The Fisher test showed $P = 0.03$ for group 0, $P = 0.01$ for group D+3, and $P = 0.03$ for group D1. There was no significant difference of tumor implantation between group D3, group D7, and control group.

Tumor volume. The mean volume of tumor implants in control group was 16.2 ($\pm$4.7) mm^3. The mean volume for groups D0, D+3, D1, D3, D7 groups were, respectively, (2.2 ($\pm$3.7) mm^3, 1.6 ($\pm$2.3) mm^3, 3.9 ($\pm$5.1) mm^3, 10.2 ($\pm$8.6) mm^3, and 12.9 ($\pm$8.5) mm^3. Rats treated before postoperative day 3 had a significantly smaller tumor volume compared to the control group. The Wilcoxon rank test showed $P < 0.001$ for group 0, $P < 0.001$ for group D+3, and $P = 0.001$ for group D1. There was no significant difference in tumor volume between group D3, group D7, and control group.

Experiment 2: Effect of Intraoperative ip Administration of rt-PA Alone on Incidence and Volume of Tumor Implants (Table I)

Incidence of implantation. Eight rats (80%) treated with intraperitoneal rt-PA alone given at the time of wounding exhibited tumor implantation in peritoneal wounds (Table I). This incidence was not significantly different from that of the control group.

Tumor volume. The mean tumor volume of implants was 9.5 ($\pm$7.9) mm^3 in rats treated with rt-PA alone. Rats treated with rt-PA alone had a significantly ($P = 0.03$, Wilcoxon rank test) smaller tumor volume compared to the control group.

Experiment 3: Combination of Intraoperative rt-PA and ip Doxorubicin in the Prevention of Tumor Implantation in Wounds (Fig. 2)

Incidence of implantation. All groups received, in addition to ip doxorubicin, an intraoperative ip injection of rt-PA. Four rats (40%) of group D0, 4 rats (40%) of group D+3, 3 rats (30%) of group D1, 6 rats (60%) of group D3, and 5 rats (50%) of group D7 demonstrated tumor deposit in the peritoneal wound. Except for group D3, all groups which received doxorubicin and intraoperative rt-PA had a significantly lower incidence of tumor implantation compared to the control group. The Fisher test showed $P = 0.01$ for group 0, $P = 0.01$ for group D+3, $P < 0.001$ for group D, and $P = 0.03$ for group D7.

Tumor volume. The mean volumes for groups D0, D+3, D1, D3, D7 were, respectively, 1.8 ($\pm$3.7), mm^3, 2.1 ($\pm$3.3) mm^3, 3.2 ($\pm$4.7) mm^3, 5.4 ($\pm$5.8) mm^3, and 6.1 ($\pm$7.4) mm^3. All rats which received intraoperative rt-PA and ip doxorubicin administered at different times postoperatively showed a significant difference of tumor volume compared to the control group. The Wilcoxon rank test showed $P < 0.001$ for group 0, $P < 0.001$ for group D+3, $P < 0.001$ for group D1, $P = 0.002$ for group D3, and $P = 0.006$ for group D7.

DISCUSSION

The first part of this study demonstrated that the timing of postoperative administration of intraperitoneal doxorubicin influences significantly the incidence and volume of tumor implants in surgical wounds. The earlier the intraperitoneal chemotherapy was started the greater were its effects on tumor implantation and tumor progression in peritoneal wounds. A single injection of intraperitoneal doxorubicin at a dose of 1 mg/kg significantly decreased the incidence and volume of tumor implants in peritoneal wounds. When administered at postoperative day 3 or 7, the same dose of intraperitoneal doxorubicin did not affect

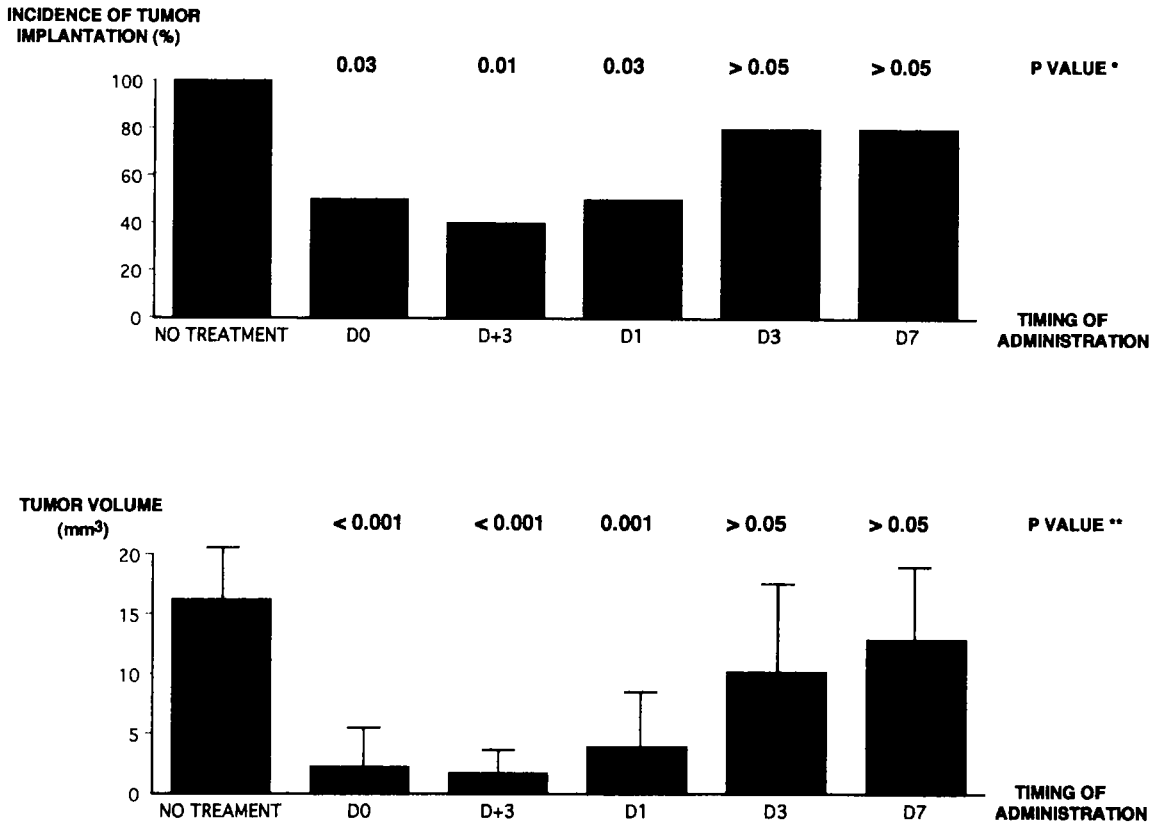

Fig. 1. Incidence and volume of tumor implants in peritoneal wounds after intraperitoneal doxorubicin administered at different times postoperatively. DO, intraoperatively; D+3, 3 hr after surgery; D1, postoperative day 1; D3, postoperative day 3; D7, postoperative day 7. *Comparison of treated group with control group (no treatment) using Fisher's test. **Comparison of treated group with control group (no treatment) using Wilcoxon test.

TABLE I. Incidence and Volume of Tumor Implants in Peritoneal Wounds of Rats With No Treatment and of Rats Treated by Intraperitoneal Injection of 5 mg/kg of rt-PA at the End of the Surgical Procedure

	Control[a]	rt-PA 5 mg/kg IP	*P*
Incidence of tumor implantation (%)	100	80	>0.05
Volume of tumor implants (mm^3)	16.2 ± 4.7	9.5 ± 5.9	0.03

rt-PA, recombinant tissue plasminogen activator.
[a]Intraperitoneal injection of 3-ml saline solution.

the implantation and the growth of tumor cells in the wound area.

Previous experimental studies have suggested that shortening the time interval between tumor resection and chemotherapy administration increased drug effectiveness [19–22]. This mechanism of tumor resistance to delayed intraperitoneal chemotherapy may be related to several factors. The most simplified explanation for the early benefit and later failure of intraperitoneal chemotherapy relates to direct exposure of tumor to drug early but deterioration of this access as wound healing progresses. Tumor cells trapped in fibrin will be increasingly sequestered in the extracellular matrix produced during the next phases of healing.

However, decreased contact between intraperitoneal chemotherapy and tumor cells entrapped in wound matrix may not be the only mechanism for diminished effects with delayed intraperitoneal chemotherapy. Fisher et al. [23,24] demonstrated that the cytotoxic effect of systemic cyclophosphamide on residual tumor after removal of a primary mammary adenocarcinoma was more pronounced if chemotherapy was given on the day of surgery or the first postoperative day. The chemotherapy was least effective when administered seven days after primary

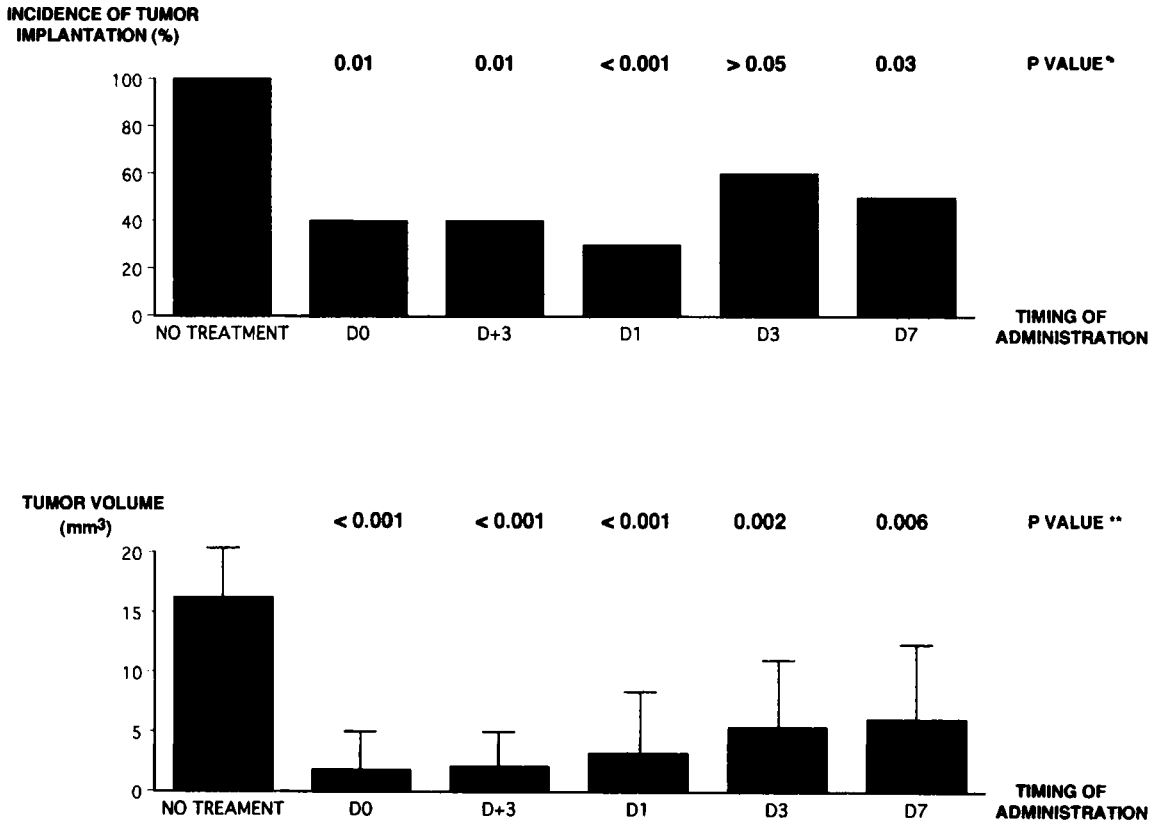

Fig. 2. Incidence and volume of tumor implants in peritoneal wounds after intraoperative rt-PA combined with intraperitoneal doxorubicin administered at different times postoperatively. DO, intraoperatively; D+3, 3 hr after surgery; D1, postoperative day 1; D3, postoperative day 3; D7, postoperative day 7. *Comparison of treated group with control group (no treatment) using Fisher's test. **Comparison of treated group with control group (no treatment) using Wilcoxon test. rt-PA, recombinant tissue plasminogen activator.

tumor excision. In that study, the labeling index of residual tumor cells was determined for each group of rats. A transient increase of cell labeling index was observed during the first 3 days following surgery. The increased labeling index was due to noncycling cells becoming proliferative and therefore becoming more vulnerable to cytostatic drugs. Fisher related the advantage of early (before day 3) postoperative chemotherapy to effects of drugs during the rapid cell proliferation resulting from surgical removal of tumor. Delay in the onset of chemotherapy required treatment of a larger tumor burden having a reduced sensitivity.

In our rat model, colon adenocarcinoma cells were directly injected into the peritoneal cavity following surgical trauma to the peritoneum. As in the Fisher's experiment, the kinetics of cell growth were likely to be increased in the early postoperative period. Surgical trauma induces a generalized state of immunodepression characterized by a release of cytokines and growth factors [25]. High levels of cytokine during the first postoperative days have been detected in peritoneal fluid of patients who underwent elective major surgery [26]. The same growth factors that modulate wound healing may promote tumor cell proliferation at the site of healing wounds. Intraperitoneal chemotherapy administered concomitantly with high levels of growth factors may abrogate the tumor cell promotion that would otherwise occur. Chemotherapy administered later postoperatively would not act with the same effectiveness on wound implants.

Another mechanism of drug resistance of wound tumor with delayed doxorubicin may be related to a higher expression of multidrug resistance (mdr) gene in tumor cells implanted for a long time in wound sites. This mdr gene expression has been shown to be influenced by the organ environment [27]. Wound microenvironment which is rich in growth factors may influence the mdr gene expression of tumor cells implanted in this area. Among the plethora of soluble factors released by monocyte and macrophages in the wound site are: the proinflammatory cytokines, such as interleukin-1 (IL-1) and tumor necrosis factor (TNF); growth factors such as fibroblast growth factors (FGF), platelet-derived growth factor (PDGF); and perhaps the most extensively studied growth factor, transforming growth factor (TGF)-β. Factors like TGF-β, interferon (IFN)-β, and IFN-γ have been shown to modulate the mdr gene expression in astrocyte and glioblastoma cell lines [28,29]. It is possible that tumor cells exposed for few days to a microenvironment rich in such

growth factors may overexpress the mdr gene, becoming more resistant to delayed administration of intraperitoneal doxorubicin.

The second aspect of our study evaluated the activity of one specific strategy to increase the effectiveness of intraperitoneal chemotherapy over time on wound tumor implants. Peritoneal injury has been shown to result in a clotting cascade activation necessary for tumor cell adherence [30,31]. Administration of agents that prevent fibrin clot formation or actively promote fibrinolysis may effectively prevent tumor cell adherence in wounds [15,32]. Among the drugs tested, rt-PA has been shown to prevent tumor implantation effectively in liver wounds [15].

In an evaluation of rt-PA alone in our model, it significantly decreased the volume of tumor implants but it did not influence significantly the frequency of tumor implantation. When administered with chemotherapy delivered on postoperative day 3 and postoperative day 7, rt-PA increased doxorubicin effects. When administered with chemotherapy delivered at the end of surgery, 3 hours later, or 1 day later, rt-PA did not change significantly the effect of doxorubicin. These results may suggest that the tumor resistance in peritoneal wound to chemotherapy administered at postoperative day 3 and postoperative day 7 is related to the presence of fibrin. Once tumor cells have adhered to the wound extracellular matrix deposit, they become covered by fibrin deposit that provide an initial source of nutrition and protect them for the host defense [33]. When intraperitoneal chemotherapy is delivered after the third postoperative day, this protein deposit may cover all tumor cells in the traumatized area and thereby prevent any contact between the intraperitoneal drug and the entrapped tumor cells. If the extracellular protein matrix is reduced by intraoperative fibrinolytic therapy, delayed intraperitoneal chemotherapy administration may still gain access to implanted tumor cells. Alternatively, rt-PA effects may be to inhibit cancer cell accumulation at the wounded site. In the absence of fibrin entrapment, tumor cells may settle on a roughened wound surface but many may release. Without an adherence site these cancer cells may be much less damaging to the host and remain vulnerable to intraperitoneal chemotherapy for several more days.

In conclusion, these findings provide a rationale for the use of intraoperative or early postoperative (before postoperative day 3) intraperitoneal chemotherapy in the prevention of tumor recurrence in wound sites. Intraperitoneal chemotherapy administered at the third postoperative day or later is less effective on tumor cells implanted in surgically traumatized area than chemotherapy administered before the third postoperative day. This observation implies that clinical studies evaluating the effectiveness of intraperitoneal chemotherapy must take into account the timing of administration as previously suggested [10,11].

In order to maintain the cytotoxic effect of delayed intraperitoneal chemotherapy toward tumor cells implanted in surgical wounds, the destruction of fibrin deposits by intraoperative administration of fibrinolytic agent may be required. Although rt-PA may cause less hemorrhagic complications than fibrinolytic agents such as streptokinase or urokinase [34], clinical use of rt-PA in the postoperative period requires cautious clinical studies because of its thrombolytic properties.

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